

Creutzfeldt-Jakob Disease in Unusually Young Patients Who Consumed Venison

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Background: Creutzfeldt-Jakob disease (CJD) in humans and chronic wasting disease (CWD) in deer and elk occur in the United States. Recent reports of 3 unusually young patients with CJD who regularly consumed deer or elk meat created concern about the possible zoonotic transmission of CWD.

Objective: To examine the possible transmission of CWD to humans.

Patients: Three unusually young patients (aged 28, 28, and 30 years) with CJD in the United States during 1997-2000.

Methods: We reviewed medical records and interviewed family members and state wildlife and agriculture officials. Brain tissue samples were tested using histopathologic, immunohistochemical, immunoblot, or prion protein gene analyses.

Main Outcome Measures: Presence or absence of established CJD risk factors, deer and elk hunting in CWD-

endemic areas, and comparison of the evidence for the 3 patients with that of a zoonotic link between new variant CJD and bovine spongiform encephalopathy.

Results: None of the patients had established CJD risk factors or a history of travel to Europe. Two patients hunted game animals and 1 was a daughter of a hunter. Unlike patients with new variant CJD, the 3 patients did not have a unique neuropathologic manifestation, clinicopathologic homogeneity, uniformity in the codon 129 of the prion protein gene, or prion characteristics different from those of classic variants.

Conclusions: Although the occurrence of 3 unusually young patients with CJD who consumed venison suggested a possible relationship with CWD, our follow-up investigation found no strong evidence for a causal link. Ongoing CJD surveillance remains important for continuing to assess the risk, if any, of CWD transmission to humans.

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CREUTZFELDT-Jakob disease (CJD) is a rapidly progressive, invariably fatal neurodegenerative disorder classified as a transmissible spongiform encephalopathy.¹ This disease, like other transmissible spongiform encephalopathies, is believed to be caused by the accumulation in neurons of an abnormal isoform of a membrane glycoprotein known as the *prion protein*. Creutzfeldt-Jakob disease occurs at an estimated annual incidence of approximately 1 case per million population. In the United States, the disease primarily affects persons aged 55 to 75 years (median age at death, 68 years).^{1,2} Creutzfeldt-Jakob disease occurs sporadically, without any recognizable pattern of transmission, in approximately 85% of patients and as an inherited disease in 5% to 15% of patients. Iatrogenic transmission of the CJD

agent has been reported in more than 250 patients worldwide through the use of contaminated cadaveric human growth hormone, neurosurgical equipment, and dura mater and corneal grafts.^{1,3,4} Sporadic CJD has recently been further characterized and subdivided into 5 distinct variants by correlating the clinical and pathologic phenotypes with the genotype at the polymorphic codon 129 of the prion protein gene (PRNP) and the size of the protease-resistant prion protein (PrP-res) fragment.⁵ The presence of these variants underscores the heterogeneity of sporadic CJD.

In 1996, a new variant form of CJD (nvCJD) in unusually young patients (median age at onset, 28 years) with a previously unrecognized distinct clinicopathologic profile was reported in the United Kingdom.^{1,6,7} Strong laboratory and epidemiologic evidence indicates that nvCJD

PATIENTS AND METHODS

Patients were identified via the ongoing nationwide CJD surveillance conducted by the Centers for Disease Control and Prevention (CDC), Atlanta, Ga. This surveillance includes review of passively reported CJD cases, analysis of national mortality data, follow-up investigation of patients younger than 55 years with CJD, and review of cases evaluated at the National Prion Disease Pathology Surveillance Center, Cleveland, Ohio. This center was established in 1997 by the American Association of Neuropathologists in collaboration with the CDC to facilitate neuropathologic surveillance of human transmissible spongiform encephalopathies in the United States. We reviewed clinical records of the patients to assess their illness presentation, laboratory findings, and disease progression. We determined the presence or absence of established CJD risk factors, travel history, details of hunting practices, and food consumption histories by interviewing close family members. We focused on possible exposures to deer or elk meat originating from the known CWD-endemic areas of Colorado and Wyoming. The Animal and Plant Health Inspection Service, US Department of Agriculture, Riverdale, Md, in cooperation with state wildlife and agriculture officials, collected hunter-harvested deer and elk brain samples from areas where the patients or their families were reported to have hunted deer or elk to evaluate the presence or absence of CWD in these areas. These brain samples were tested by immunohistochemistry at the National Veterinary Services Laboratories, Animal and Plant Health Inspection Service, US Department of Agriculture, Ames, Iowa.

Fixed cortical sections of the brain obtained at autopsy and a blood sample were available for testing for patient 1; fixed and unfixed brain tissue samples obtained at biopsy and autopsy were available for patient 2; and fixed and unfixed brain tissue samples obtained at biopsy were available for patient 3. Tissue samples were examined at the National Prion Disease Pathology Surveillance Center. Histopathologic and immunohistochemical examinations and sequencing of the open reading frame of the *PRNP* were performed on tissue samples from all 3 patients. Immunoblotting of the PrP-res fragment was done for patients 2 and 3 but not for patient 1 because frozen brain tissue samples were unavailable. Immunohistochemical and immunoblot analyses were performed using the monoclonal antibody 3F4 to prion protein residues 109-112. The laboratory methods used in the histopathologic, immunohistochemical, immunoblot, and genetic analyses have been described elsewhere.^{5,11} Cerebrospinal fluid examination for the presence of the 14-3-3 protein was performed for patients 2 and 3 according to methods described by Hsich et al.¹²

is causally linked to an outbreak of bovine spongiform encephalopathy (BSE).⁷ The presumed transmission of BSE to humans through food consumption causing nvCJD has focused attention on the possibility that chronic wast-

ing disease (CWD) in deer and elk could be transmitted in a similar way.

Chronic wasting disease was first recognized in 1967 in captive deer at wildlife research facilities in Colorado. Subsequently, its occurrence in free-ranging deer (*Odocoileus* species) and elk (*Cervus elaphus*) was reported in Colorado and Wyoming. Results of random pre-clinical testing of harvested animals indicated that CWD occurs almost exclusively in a contiguous 38 137-km² area in northeastern Colorado and southeastern Wyoming.⁸⁻¹⁰ The overall CWD prevalence in mule deer in the endemic area during 1996-1999 was 4.9%; the prevalence in elk was less than 1%.¹⁰ Chronic wasting disease in free-ranging deer or elk has not been detected in more than 10 states outside of the endemic areas in which surveys have been conducted, except for 1 CWD-positive deer from southwestern Nebraska, a few kilometers across the border from the known CWD-endemic areas of Colorado and Wyoming. Occurrence of CWD in privately owned captive elk herds has been reported in Colorado, Nebraska, Oklahoma, Montana, South Dakota, and Saskatchewan.^{8,9}

To explore the possible zoonotic transmission of the CWD agent, we investigated 3 unusually young patients with CJD who were reported to have regularly consumed deer or elk meat. We summarize the clinical, epidemiologic, and laboratory findings and present the available evidence regarding a possible causal link between CWD and CJD in these patients.

RESULTS

Between January 1, 1997, and May 31, 2000, 2 patients with CJD aged 28 years and 1 aged 30 years with a history of venison consumption were reported to the CDC (**Table 1**). None of the patients had established CJD risk factors, such as a family history of CJD, receipt of human growth hormone or dura mater or corneal grafts, or a previous neurosurgical procedure. In addition, none of the patients had traveled to Europe. Two patients were hunters and regularly consumed game meat. The third patient was not a hunter but consumed venison from game animals hunted by family members. Comparison of key evidence for a possible causal link between the 3 patients' illness and CWD with that of patients with nvCJD and BSE in the United Kingdom is shown in **Table 2**.

PATIENT 1

In early 1997, a 28-year-old woman was examined several times in an emergency department for abnormal mental status, weakness, and unsteady gait. She also developed ataxia, dyskinesia, and marked dysarthria. The patient's condition gradually deteriorated, and she was admitted to a community hospital in March 1997. On admission, the patient had lethargia, athetoid and choreoform movements, constant lip smacking, possible hallucination, and increased muscle tone. After hospital admission, she developed primitive frontal release signs and episodic focal seizures. The electroencephalogram showed a severely abnormal tracing with diffuse, slow triphasic waves. The computed tomographic scan and

Table 1. Selected Clinical and Laboratory Findings in 3 Unusually Young Patients With CJD Who Had a History of Regular Venison Consumption, United States*

Characteristic	Patient No.		
	1	2	3
Year of death	1997	1999	2000
Age at death, y	28	30	28
Sex	Female	Male	Male
Clinical presentation	Abnormal mental status, unsteady gait	Progressive cognitive difficulties	Loss of memory, behavioral change, confusion
Illness duration, mo	4	10	15
Histopathologic findings	Widespread spongiosis and astrogliosis in cortical and subcortical regions of the brain, moderate loss of neurons	Prominent spongiosis and gliosis in the cerebral cortex and basal ganglia, occasional ballooned neurons	Spongiosis, astrogliosis, and possible neuronal loss in the cerebral cortex (biopsy tissue sample)
Immunohistochemical findings	Strong immunostaining, "synaptic" pattern	Weak immunostaining, synaptic pattern	Questionable immunostaining, possibly synaptic pattern†
Immunoblot pattern	Not done	Type 1	Type 1
Codon 129 analysis	<i>Met/Met</i>	<i>Val/Val</i>	<i>Met/Val</i>

*CJD indicates Creutzfeldt-Jakob disease; Met, methionine; and Val, valine.

†Immunohistochemical analysis for patient 3 was performed on a brain biopsy tissue sample obtained early in the course of the illness.

magnetic resonance image of the brain did not reveal any abnormality. A brain biopsy performed to evaluate a suspected CJD diagnosis showed only gliosis. The patient died in June 1997, almost 4 months after the onset of illness.

Histologic examination of brain tissue samples obtained at autopsy showed widespread spongiform degeneration involving the cerebral cortex. The spongiosis was associated with astrogliosis and moderate loss of neurons. The lesions seemed to be more prominent in the frontal lobe and in the entorhinal cortex. The basal ganglia; the thalamus, especially the mediodorsal nucleus; the tectum of the midbrain and pons; the substantia nigra; and the molecular layer of the cerebellar cortex all showed spongiosis and astrogliosis. Immunohistochemical examination for prion protein residues demonstrated a strong and consistent "synaptic" or "punctate" pattern of immunostaining in the cerebral cortex. Rarely, the immunostaining showed a preferential perineuronal distribution that involved both cell body and processes. Analysis of the *PRNP* indicated a *Met/Met* homozygosity at the polymorphic codon 129 and absence of genetic mutations.

The patient's mother indicated that the patient had worked as a cashier at different department stores and a fast food restaurant. She had undergone tonsillar surgery at age 5 years. Her regular diet included consumption of beef, pork, and chicken several times a week. She might have consumed lamb or mutton once every several years. In addition, the patient consumed deer meat between ages 1 and 6 years. The deer were harvested mostly from Maine by the patient's father but occasionally from New Jersey by other family members. The deer carcasses were usually prepared by a custom processor. The patient primarily consumed the deer meat as steaks and ground meat mixed into sauce. At about 6 years of age, the patient had also consumed elk meat provided by a family friend as a gift on 2 different occasions. Although the origin of the elk could not be clearly ascertained, a family member reported that it was likely har-

Table 2. Comparison of Key Evidence Supporting a Causal Link Between BSE and nvCJD in the United Kingdom With That of CWD and Unusually Young Patients With CJD in the United States*

	BSE/nvCJD†	CWD/CJD
Increasing incidence in young individuals	Definite	Not definite
Phenotypic homogeneity among case-patients	Yes	No
Distinctive neuropathologic manifestation	Yes	No
Protease-resistant prion protein immunoblot characteristics different from classic variants	Yes	No
Definite consumption of food derived from animals in endemic/epidemic areas	Yes	No
Polymorphism at codon 129 of the prion protein gene	<i>Met/Met</i> (exclusively)	Heterogeneous

*BSE indicates bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; nvCJD, new variant CJD; CWD, chronic wasting disease; and Met, methionine.

†Data are from Belay,¹ Will et al,⁶ and Schonberger.⁷

vested in Wyoming. The patient was also reported to have occasionally consumed meat from squirrel, bear, and rabbits. No consumption of brain or organ meat from domesticated or game animals was reported.

PATIENT 2

In September 1998, a 29-year-old man was examined at a university hospital for progressive cognitive difficulties. His illness began in May 1998, when he experienced difficulty completing his travel expenses after a routine business trip. The patient became increasingly forgetful, with inability to recall his wife's name, his own home telephone number, and names of long-time fam-

ily friends. In August 1998 the patient resigned from his job because of the cognitive problems. Subsequently, he developed behavioral problems and difficulties with speech, writing, naming objects, and dressing without assistance. The patient was ambulatory without imbalance but had dysmetria, tremors, and occasional myoclonus. Findings from the initial 2 electroencephalograms, the computed tomographic scan, and cerebral angiographic studies were normal. The magnetic resonance image showed cerebral atrophy without any other abnormalities. Single-photon emission computed tomographic imaging of the brain revealed a nonspecific, asymmetric, diminished perfusion over the left parietal lobe. Results of initial cerebrospinal fluid analysis for 14-3-3 protein were negative in November 1998. A brain biopsy performed in November 1998 showed diffuse spongiform encephalopathy consistent with CJD. The patient died at age 30 years in March 1999, almost 10 months after the onset of illness.

Histologic examination of the brain tissue samples obtained at autopsy showed prominent spongiform degeneration and gliosis with possible neuronal loss in the cerebral cortex and basal ganglia. In contrast, the cerebellum showed virtually no pathologic changes. The spongiosis often displayed a laminar distribution that affected the deep cortical regions. Neurons that were moderately ballooned were occasionally seen in the cerebral cortex. The pattern of prion protein immunostaining was exclusively "synaptic" in the cerebral cortex and basal ganglia, whereas the cerebellum was virtually unstained. Analysis of the *PRNP* indicated that the patient was homozygous for valine at the polymorphic codon 129. No *PRNP* mutation was detected. Immunoblot analysis showed that the PrP-res fragment migrated to 21 kd, corresponding to the prion protein type 1.

His past occupations included working as a stock boy in a grocery store and recently as a salesperson. The patient had undergone a hernia repair during infancy and tonsillar surgery at approximately 10 years of age. His regular diet included consumption of beef many times a week and pork several times a week. He occasionally ate mutton and cow brain, approximately once every several years. The patient was described as a regular hunter, hunting almost every year since 1985. He was reported to have hunted deer and elk in many areas, almost always in Utah. He did, however, hunt an elk in the southwestern part of Wyoming in 1995 and was part of a team that hunted deer around Williams Lake, British Columbia, in 1989. The patient usually field dressed the carcasses himself and took them to a particular plant for custom processing. In addition, the family has many times received gifts of deer and elk meat from the patient's brother, who regularly hunted in Utah. The family usually ate the deer and elk meat as steak, ground meat, and jerky almost once a month. Moreover, the patient regularly ate liver from deer and elk but not other organ meat, including brain, from any game animals.

PATIENT 3

In December 1998, a 27-year-old man began experiencing difficulty finding his hometown and lapses in memory

while performing his duties as a truck driver. During the next month, the patient became increasingly forgetful, constantly asking for directions and instructions on how to operate the truck. He started to exhibit impulsive and impatient behavior, the inability to dress properly, difficulty finding words, and confusion. He also developed myoclonus and sleep disturbances. The electroencephalographic tracing was abnormal but nondiagnostic. The magnetic resonance image of the brain showed diffuse cortical hyperintensity with an unusual but nonspecific pattern. Findings from the cerebrospinal fluid 14-3-3 immunoassay were positive. Histopathologic examination of the cerebral cortical tissue samples obtained at biopsy revealed widespread spongiform degeneration associated with astrogliosis and a possible loss of neurons. Analysis of the *PRNP* indicated a *Met/Val* heterozygosity at codon 129 and absence of *PRNP* mutations. Immunoblot analysis showed that the PrP-res fragment migrated to 21 kd, in the polyacrylamide gel corresponding to the prion protein type 1. The patient died in April 2000 at age 28 years, almost 15 months after the onset of illness. No autopsy was performed.

His occupations included driving a truck locally and spreading fertilizers. Since 1993 he had also been assisting his father-in-law in raising beef cattle. The patient had no history of surgical procedures. His regular diet included consumption of beef, pork, and chicken several times a week. No consumption of lamb or mutton was reported. The patient was described as an "avid hunter," hunting deer regularly since age 13 years, and frequently harvested at least 1 deer annually. Almost all his deer hunting took place exclusively in 2 very localized areas within 2 counties close to his hometown. The patient usually field dressed the deer carcasses himself and took them to a particular plant for custom processing. During the previous 6 years, the patient and his family had reportedly consumed only ground venison almost once a month. During his childhood, the patient also consumed deer meat harvested by his father. The patient's wife reported no consumption of deer or elk meat originating from either Colorado or Wyoming. However, the custom processing plant where the patient regularly took the deer carcasses for processing also processed approximately 20 elk from Colorado every year. The exact geographic origin in Colorado of these elk could not be ascertained. No consumption of brain or other organs from domesticated or game animals was reported. On the basis of hunter survey data obtained from the local Department of Wildlife Conservation, the patient's hunting practices were typical of other game animal hunters in the area. Analysis of the 1998 hunter licensing data estimated that approximately 24% of families and approximately 17% of households in the state might include a licensed hunter.

COMMENT

In the United States, the occurrence of CJD in persons 30 years or younger is rare. During 1979-1996, only 12 CJD cases in this young age group were reported to the CDC. The occurrence of CJD in unusually young patients is generally regarded as a warning signal for an ex-

ogenous source of infection. Eight of the 12 US CJD cases in persons 30 years or younger resulted from the use of contaminated human growth hormone or dura mater grafts. After surveillance for young patients with CJD was increased in 1996 owing to concern about nvCJD, the 3 young patients described in this study constituted all but 1 of the sporadic CJD cases in persons 30 years or younger reported in the United States through May 31, 2000. The fourth unusually young patient with CJD was homozygous for valine and predominantly had cerebellar dysfunction and an illness duration of approximately 5 years; the patient was not a hunter and did not have a history of venison consumption. Nevertheless, the occurrence since 1996 of the 3 patients described in this study created concern about a possible zoonotic transmission of CWD primarily because of their unusually young age, absence of established CJD risk factors, and frequent consumption of deer or elk meat.

In the United Kingdom, the occurrence of a cluster of 10 unusually young patients with CJD (median age, 28 years) during 1994-1995 prompted investigators to explore the possible transmission to humans of the BSE agent that was causing a widespread epidemic in cattle in the United Kingdom for more than 10 years.⁶ The UK government's conclusion that the illness in these unusually young patients might have been causally linked to BSE was later strengthened by additional epidemiologic and laboratory evidence.¹ These key lines of evidence supporting a causal link between BSE and nvCJD in the United Kingdom were compared with those of a possible link between CWD and CJD in the 3 young US patients (Table 2). The nvCJD was notable for a definite increase of the disease in unusually young patients. Through February 2001, 57 (67%) of 85 patients with nvCJD died at 30 years or younger in the United Kingdom (R. G. Will, MD, oral communication, February 2001).¹³ In contrast, no definite increase of unusually young patients with CJD was documented in the United States despite increased surveillance for young patients with CJD since 1996. Among the nvCJD cases, a unique but uniform neuropathologic profile was reported, including spongiform lesions most evident in the basal ganglia and the presence of multiple plaques characterized by a halo of surrounding spongiform lesions, resembling the "florid" plaques described in experimental transmission of Icelandic scrapie in mice.¹⁴ In contrast, the neuropathologic manifestation in the 3 US young patients was not different from that previously documented for patients with sporadic CJD.⁵ In patients with nvCJD, the immunoblot characteristics of the PrP-res fragment were distinct from those of PrP-res obtained from patients with sporadic CJD. In at least 2 of the patients we investigated (patients 2 and 3), however, the PrP-res fragment was shown to have the type 1 immunoblot pattern similar to that reported in about 71% of patients with sporadic CJD.⁵ All the reported patients with nvCJD had *Met/Met* homozygosity at codon 129 of the *PRNP*, whereas each of the 3 patients in our study had the different polymorphisms at codon 129 (Table 1).

On the basis of a sporadic CJD classification scheme developed by Parchi et al,⁵ patients 2 and 3 would have been classified into 2 distinct groups, VV1 and MM1/

MV1 variants, respectively. Patient 1 had *Met/Met* homozygosity at the polymorphic codon 129, but the immunoblot was not performed because of lack of frozen brain tissue samples. However, the CJD phenotype in this patient was consistent with that of the MM1/MV1 variant. The MM1/MV1 variant is the most common and represents approximately 70% of sporadic CJD cases. In comparison, the VV1 variant represents approximately 1% of sporadic CJD cases. Because of the similar characteristics between patients with the VV1 variant and patient 2, we explored the possibility that the 4 other patients with this variant reported to date might have also hunted game animals or consumed venison. Three of the cases were reported in Germany and the fourth was in the United States (H. A. Kretzschmar, MD, written communication, August 2000).¹⁵ None of the 4 patients were game animal hunters, and 2 of the 4 had no history of venison consumption.

The most frequent exposure to game animals in all 3 patients was consumption of deer meat. However, none of the deer consumed by the patients originated from the CWD-endemic areas of Wyoming and Colorado. In addition, immunohistochemical analysis identified no CWD among 1037 hunter-harvested deer and elk brain samples collected during the 1999 hunting season from the areas where the deer meat consumed by patient 1 (299 deer samples), patient 2 (404 deer and 196 elk samples), and patient 3 (138 deer samples) originated (L. A. Detwiler, DVM, e-mail communication, April 2000). Although our investigation did not document exposure to game animals specifically from the CWD-endemic counties of Wyoming and Colorado, patients 1 and 2 had a history of possible or recent exposure, respectively, to elk meat from Wyoming. The elk meat consumed by patient 1 and her family on 2 different occasions when the patient was aged approximately 6 years was reported to have possibly been harvested by a family friend from Wyoming. The Wyoming origin of the elk was based on a vague recollection by the patient's mother, and we were unable to trace and independently verify the origin by interviewing the family friend. The elk meat consumed by patient 2 and his family was reportedly harvested by the patient from southwestern Wyoming during the 1995 hunting season. However, the exposure to elk meat in 1995 implies an incubation period of less than 3 years, which seems to be too short for the oral route of exposure. In addition, no cases of CWD were reported in the southwestern part of Wyoming where the patient hunted the elk.¹⁰ For patient 3, the only plausible exposure to deer or elk meat from CWD-endemic states that our investigation uncovered was the possibility that his deer meat could have been contaminated at the custom processing plant with elk meat harvested from Colorado and processed in the same plant. It remains uncertain whether any of the elk processed in the plant were infected or originated from Colorado counties known to have endemic CWD.

Although the occurrence of CJD in 3 unusually young persons who regularly consumed deer and elk meat and had no known CJD risk factors suggested a possible link to CWD, our investigation found no strong evidence for a causal association between CWD and CJD.

None of these patients had a definite history of consumption of deer or elk meat obtained from the CWD-endemic areas. In addition, the lack of homogeneity in the polymorphic codon 129 of the PRNP and phenotypic expression of the disease suggest that a causal link between CWD and CJD in the 3 patients is unlikely. Rather, the results of our investigation indicate that the association of the 3 unusually young CJD cases with game animal hunting or venison consumption was more likely coincidental than causal. Venison consumption is not uncommon in the United States. In a survey conducted by the American Red Cross and other blood banking establishments, 40% of US blood donors reported consumption of deer or elk meat obtained from the wild.¹⁶ On the basis of such a prevalence of venison consumption, a history of consumption of deer or elk meat in 3 of the 4 patients with sporadic CJD 30 years or younger reported in the United States after March 1996, when surveillance for young patients with CJD was increased, could reasonably have occurred by chance alone. Nevertheless, to further assess the possibility that the CWD agent might occasionally cause disease in humans, additional laboratory studies could be helpful, including molecular characterization and strain typing of the agents causing CWD in deer and elk and CJD in potentially exposed patients. Ongoing national surveillance of CJD will remain important for continuing to assess the risk, if any, of CWD transmission to humans.

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